



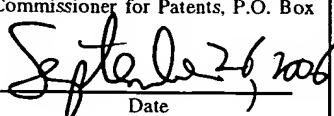
CASE: LA0112 NP

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Burton Rodney  
Type or print name

Signature

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ART UNIT: 1626

**TIMUR GUNGOR, ET AL.**

EXAMINER: STOCKTON, LAURA LYNNE

APPLICATION NO: **10/775,742**

FILED: **02/10/2004**

FOR: **NOVEL THIAZOLIDINE COMPOUNDS AS CALCIUM  
SENSING RECEPTOR MODULATORS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

DECLARATION OF YING CHEN

To the Commissioner for Patents and Trademarks:

YING CHEN DECLARES AS FOLLOWS:

1. He has a Master's degree in Organic Chemistry and is a medicinal chemist specializing in the preparation of organic compounds.

2. He was employed in the above capacity at Bristol-Myers Squibb Company for more than 9 years, and worked under the supervision of Dr. Timur Gungor at Bristol-Myers Squibb Company.

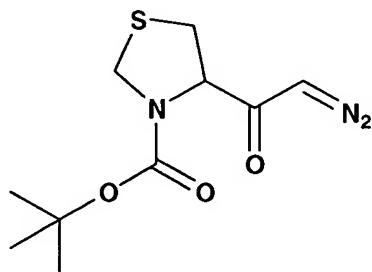
**BEST AVAILABLE COPY**

3. He was asked by Dr. Gungor to prepare the compounds which were eventually covered in the subject patent application including Example 1 thereof.

4. That he is not an inventor of the invention claimed in U.S. patent application Serial No. 10/775,742 filed February 10, 2004.

5. That prior to October 22, 2001, experiments were carried out by him under the supervision of Timur Gungor to prepare compounds covered by the claims of the subject application, including the compound of Example 1, which experiments were recorded in Bristol-Myers Squibb Notebook No. 48255 cover page (ATTACHMENT C) and pages 101, 102, 103, 104, 105 and 108, copies of which pages are attached hereto and identified as ATTACHMENTS D, E, F, G, H and I', respectively.

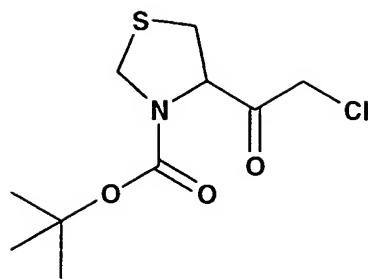
6. On Notebook page 48255-101 (hereinafter page 101) (ATTACHMENT D), entitled Proj. No. 08001, he recorded the preparation of intermediate



from Boc-D-thiazolidine-4-carboxylic acid, which experiment he carried out prior to October 22, 2001.

Page 101 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

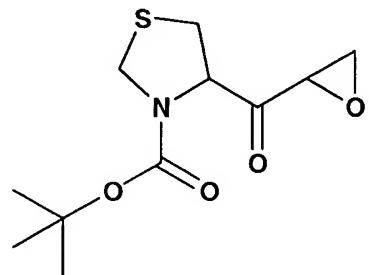
7. On Notebook page 48255-102 (hereinafter page 102) (ATTACHMENT E), entitled Proj. No. 08001, he recorded the preparation of the chloride intermediate



prepared from the intermediate prepared as recorded on page 101 (ATTACHMENT D), which experiment was carried out prior to October 22, 2001.

Page 102 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

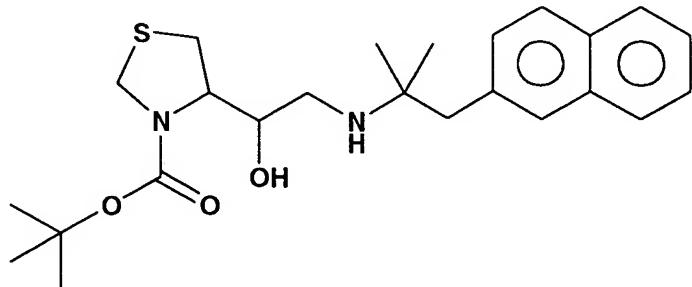
8. On Notebook page 48255-103 (hereinafter page 103) (ATTACHMENT F), entitled Proj. No. 08001, he recorded the preparation of the intermediate



prepared from the chloride intermediate prepared as recorded on page 102 (ATTACHMENT E), which experiment was carried out prior to October 22, 2001.

Page 103 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

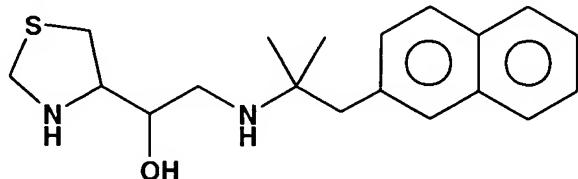
9. On Notebook page 48255-104 (hereinafter page 104) (ATTACHMENT G), entitled Proj. No. 08001, he recorded the preparation of the intermediate



prepared from the intermediate prepared as recorded on page 103 (ATTACHMENT F), which experiment was carried out prior to October 22, 2001.

Page 104 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

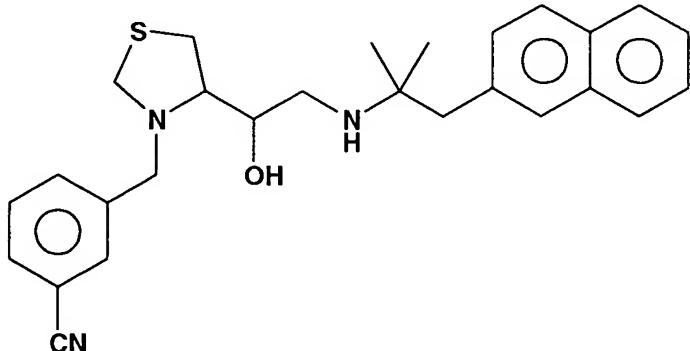
10. On Notebook page 48255-105 (hereinafter page 105) (ATTACHMENT H), entitled Proj. No. 08001, he recorded the preparation of the intermediate



prepared from the intermediate prepared as recorded on page 104 (ATTACHMENT G), which experiment was carried out prior to October 22, 2001.

Page 105 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

11. On Notebook page 48255-108 (hereinafter page 108) (ATTACHMENT I'), entitled Proj. No. 08001, he recorded the preparation of the compound of Example 1 of the subject application



prepared from the intermediate prepared as recorded on page 105 (ATTACHMENT H), which experiment was carried out prior to October 22, 2001.

Page 108 was signed by him and witnessed by Hao Zhang, prior to October 22, 2001.

12. The actual dates of the experiments regarding the preparation of the Example 1 compound recorded in Notebook No. 48255-101, 102, 103, 104, 105, 108 were carried out and the dates of signing by him and witnessing by Hao Zhang, were all prior to October 22, 2001, but have been obliterated.

13. This Declaration is submitted prior to Final Rejection.

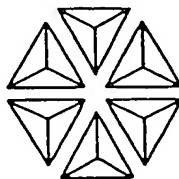
14. The undersigned declares further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 10/775,742 or any patent issued thereon.

Date:

9/26/06

  
YING CHEN

PROPERTY OF  
BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE



**BRISTOL-MYERS SQUIBB**

NOTEBOOK No. 48255

Ying Chen  
AMGEN

Assigned to Ying Chen

Subject \_\_\_\_\_

Department Name \_\_\_\_\_

Department Number \_\_\_\_\_

Date Assigned 7-1-01

Date Completed \_\_\_\_\_

Pages Completed from \_\_\_\_\_ to \_\_\_\_\_

Continued from Notebook Number \_\_\_\_\_

Continued in Notebook Number \_\_\_\_\_

This notebook cannot be transferred to another person

ATTACHMENT C

## BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

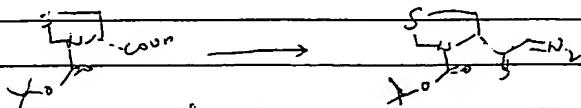
No. 48255-101

DATE: \_\_\_\_\_

PROJ. NO. *28107*

EXPT. NO. \_\_\_\_\_

SUBJECT \_\_\_\_\_



Boc-D-thiolidine 5.0 g 21.4 mmol

5 -4-carboxylic acid

isobutylchloroformate 2.76 ml 21.4 mmol

Et<sub>3</sub>N 30 ml 21.4 mmol

THF 50 ml

MNNG 11.7 g

10 KOH/H<sub>2</sub>O 15 g in 37 mlEt<sub>2</sub>O 125 ml

To a two phase solution of KOH and Et<sub>2</sub>O at 0°C was added MNNG portionwise. The ether layer was decanted to a flask.

The fresh made CH<sub>2</sub>N<sub>2</sub> in Et<sub>3</sub>N was kept at 0°C.

To a solution of Boc-D-thiolidine-4-carboxylic Acid, Et<sub>3</sub>N in THF at -10°C (acetone + ice) was added dropwise isobutylchloroformate. The reaction was kept at -10°C for 30 min then filtered (white solid was resulted from Et<sub>3</sub>N·HCl). The

filtrate was stirred at -10°C. A solution of CH<sub>2</sub>N<sub>2</sub> in Et<sub>2</sub>O was

added. Stirring was continued for 1 h. Then warmed to RT.

Et<sub>2</sub>O was added and the solution washed with H<sub>2</sub>O, Satd Na<sub>2</sub>SO<sub>4</sub> brine and dried over MgSO<sub>4</sub>. Evaporation gave a yellow oil.

Purification was performed by flash column on silica gel, loaded with chro., eluted with 25% Et<sub>2</sub>O in hexane. Pure fractions were combined and evaporated to give a pale yellow oil.

~~08/05/05~~ 48255-101-27 4.44 g (80.7%)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) was consistent  
<sup>13</sup>C NMR

LC-MS M+23 = 280

RQ 22912 for MS M+1 = 258

OK

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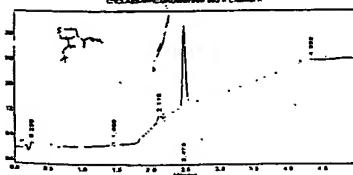
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Item No.

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Instrument: KPM-1027-LCMS1  
Well = 192 Inj. Vol. = 10 μL  
Start % B = 0  
Final % B = 100  
Gradient Time = 4 min  
Flow Rate = 0.2 mL/min  
Wavelength = 220  
Solvent A = 10% MeOH - 90% H<sub>2</sub>O - 0.1% TFA  
Solvent B = 90% MeOH - 10% H<sub>2</sub>O - 0.1% TFA  
Column 2: Phenomenex ODS 4.6 x 50 mm 14 min

48255-101



All Results

RT	Area	Area %	Plates
0.26	31325	3.367	143
1.47	27409	2.946	2324
1.50	27402	4.000	7235
2.47	65927	19.001	11273
4.33	359915	38.482	0

SIGNED

*Yan*

DATE

WITNESSED AND  
UNDERSTOOD BY

DATE

ATTACHMENT D

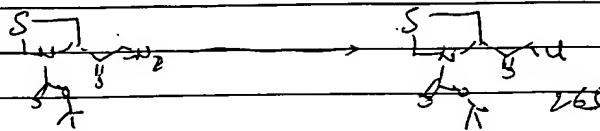
CROSS REFERENCES:

No. 48255-102

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

DATE: \_\_\_\_\_ PROJ. NO. 08001 EXPT. NO. \_\_\_\_\_

SUBJECT \_\_\_\_\_



5      48255-101-27      44 g  
HCl (4N)      5 ml  
CH<sub>2</sub>Cl<sub>2</sub>      10 ml

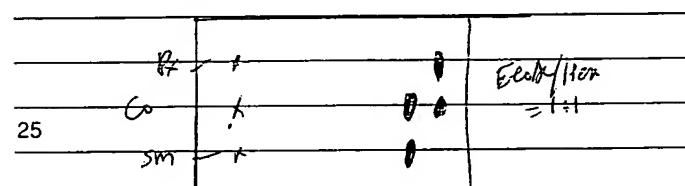
To a solution of 48255-101-27 in CH<sub>2</sub>Cl<sub>2</sub> at -10°C, a solution of 44 g HCl in diethyl ether was added dropwise (a lot of bubbles). The reaction was stirred at -10°C for 30 min. HCl was evaporated by a vacuum pump without heating. The rest of solution was warmed to RT. Evaporation to silent heat to give a yellow oil. 4.4 g

48255-101-28

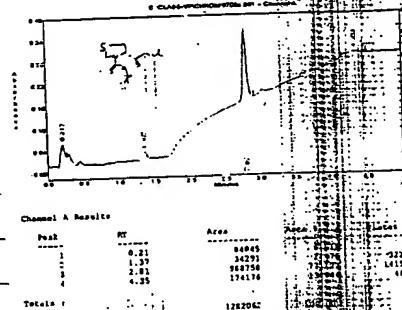
15      CC-HR mp = 288  
<sup>1</sup>H NMR were consistent.  
<sup>13</sup>C NMR

RQ 22935. TR 27235 M-1 = 263.9

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File: C:\VCLAB\7-VP\CH2Cl2.0705C.UV  
Instrument = HPM-L144-LCNS  
Well = 192      Inj. Vol. =  
Start : B = 0  
Final : B = 100  
Gradient Time = 3 min  
Rate = 1 ml/min  
Wavelength = 220  
Solvent A = 10% MeOH - 90% H<sub>2</sub>O  
Solvent B = 90% MeOH - 10% H<sub>2</sub>O  
Column 1 : Phenomenex Luna C18 5 μm, 250 × 4.6 mm, 100 Å, 100%  
48255-102



Channel A Results	
Peak	RT
	6.21
	11.27
	11.31
	11.35
Total	1282042

35

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*VJL*

DATE

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CROSS REFERENCES:

ATTACHMENT E

## BFETOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

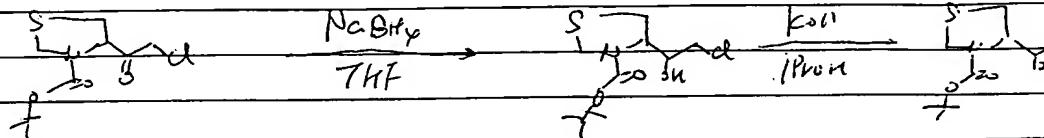
No. 48255-103

DATE: \_\_\_\_\_

PROJ. NO. 0801

EXPT. NO. \_\_\_\_\_

SUBJECT \_\_\_\_\_



5      48255-102-1X      4.4 g      16.6 mmol  
 NaBH4      614 mg      16.6 mmol  
 THF      30 mL

To a solution of 48255-102-1X in THF at RT was added NaBH4. The reactor was stirred at RT for 30 min. LC-ms showed 5M left. H2N was added to quench the reaction. EtOH was added and the solution was washed with sat'd NaHCO3, brine and dried over MgSO4. Evaporation gave a crude oil. 48255-103-13

[LC-ms showed right M+2] = 2% two isomer ratio 3:1

15      To a solution of 48255-103-13 in iPrOMe (10 mL) was added 4M KOH (10 mL). The mixture was stirred at RT for 1 h. EtOH was added and the organic layer was washed with sat'd NaHCO3, brine and dried over MgSO4. Evaporation gave a crude oil. 48255-103-18

<sup>1</sup>H NMR showed the isomer ratio = 2:1

20      Purification was performed by flash chromatography on silica gel, loaded with crude, eluted with 8% EtOAc in hex. Pure fractions were combined and evaporated to give a colorless oil ~~mp~~

Isomer I      48255-103-23      1.2 g

<sup>1</sup>H NMR and <sup>13</sup>C NMR were consistent.

25      RQ 23050, TR 27387 ms. m+1 = 232.

Isomer II      48255-103-27      1.6 g

RQ 23050

TR 27390 m+1 = 232

30

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*Y. L.*

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WITNESSED AND  
UNDERSTOOD BY:

*Stewart*

DATE -

CROSS REFERENCES:

ATTACHMENT F

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No. 48255-104

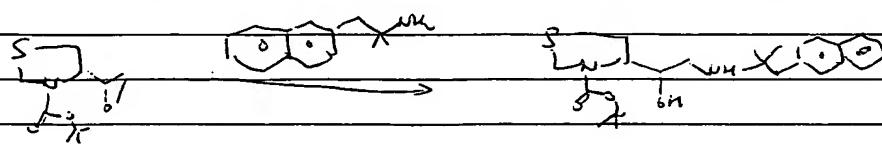
BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

DATE: \_\_\_\_\_

PROJ. NO. 08067

EXPT. NO. \_\_\_\_\_

SUBJECT \_\_\_\_\_



5

48255-103-23      500 mg      2.17 mmol  
 Amine                432 mg      2.17 mmol

The mixture of 48255-103-23 and amine was heated together at 90°C for 3 hr. TLC and LC-MS showed no epoxide & left. The reaction was cooled to RT. Purification was performed by flash chromatography on silica gel, loaded with crude, eluted with 3% MeOH in CHCl<sub>3</sub> + 0.2% NH<sub>3</sub> aq. Pure fractions were combined and evaporated to give a colorless oil.

48255-103-16 833 mg (89%)

RQ 23057 BMS-538174-01

15

ms (TR 273.94) m+1 = 93

411m/z very consistent.  
13C NMR

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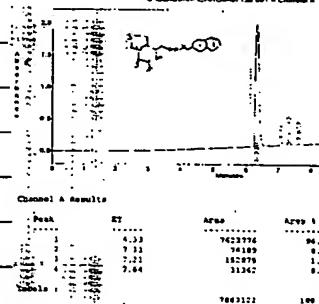
## Analytical HPLC Report

File # C:\CLASS\VF\CHROM\0712d.001

7/24/91

Instrument: HPM-L112-HPLC  
 Soln. = 100 Inj. Vol. = 10 μL  
 Start % B = 0  
 Final % B = 100  
 Gradient Time = 8 min  
 Flow Rate = 2.5 mL/min  
 Wavelength = 220  
 Solvent A = 10% MeOH - 90% H<sub>2</sub>O - 0.2% H<sub>3</sub>PO<sub>4</sub>  
 Solvent B = 90% MeOH - 10% H<sub>2</sub>O - 0.2% H<sub>3</sub>PO<sub>4</sub>  
 Column 1: Zorbax SB-C18 4.6mm ID x 75mm 10 MIN

48255-103-16



## Channel A Results

Pkt.	Area	Area %	RT[min]
1	700.000	96.127	16.037
2	2.000	0.002	16.037
3	24.000	1.027	16.037
4	182.070	1.323	16.037
5	33.340	0.338	16.037
	7863122	100.000	

30

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*[Signature]*

DATE - 1 - 1

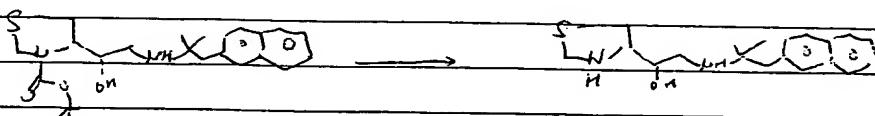
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CROSS REFERENCES:

ATTACHMENT G

## BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

No. 48255-105

DATE: \_\_\_\_\_ PROJ. NO. 08007 EXPT. NO. \_\_\_\_\_  
SUBJECT \_\_\_\_\_

5      48255-104-14      803 mg  
       HCl in dioxane      20 ml  
       THF                  10 ml

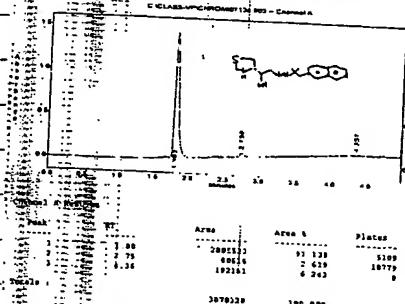
To a solution of 48255-104-14 in THF at RT was added 4N HCl  
 10 in dioxane. The reaction was stirred at RT for 24 hr.  
 Then evaporated to dryness. The residue was dissolved in EtOAc, washed  
 with water and the organic layer was washed with brine and dried over  
 MgS0<sub>4</sub>. Evaporation gave a pale-yellow oil.

48255-105-14

15      <sup>1</sup>H NMR were consistent, RQ  
       <sup>13</sup>C NMR

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*Analytical HPLC Report*  
 File: C:\CLASS\VP\CHROM\10713e.003  
 Sample ID: hel  
 Acquired: Jul 13, 2001 09:13:27  
 File Desc: User = chemv  
 Instrument = HPM-L132-HPLC  
 Method: 161      Inj. Vol. = 10 µL  
 Start #: 0  
 Final #: 100  
 Gradient Time = 4 min  
 Flow Rate = 4 mL/min  
 Wavelength = 220  
 Solvent A = 10% MeOH - 90% H<sub>2</sub>O - 0.2% NH<sub>4</sub>PO<sub>4</sub>  
 Solvent B = 90% MeOH - 10% H<sub>2</sub>O - 0.2% NH<sub>4</sub>PO<sub>4</sub>  
 Column 1: YMC 55 ODS 50 x 4.6 mm Ballistic (4)



Time	Area	Area %	Plates
10.00	2005132	93.12%	1199
10.00	1070320	6.87%	10779
10.00	1070321	0.00%	0
10.00	1070322	0.00%	0
10.00	1070323	0.00%	0
10.00	1070324	0.00%	0
10.00	1070325	0.00%	0
10.00	1070326	0.00%	0
10.00	1070327	0.00%	0
10.00	1070328	0.00%	0
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BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

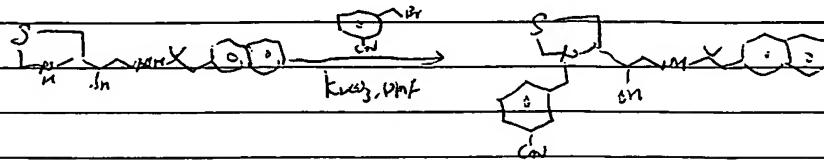
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PROJ. NO.

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EXPT. NO.

SUBJECT



5            48255-105-14        100 mg        0.3 mmole  
            $\omega$ -bromo toluenitrile        60 mg        0.3 mmole  
           K<sub>2</sub>CO<sub>3</sub>        42 mg        0.3 mmole  
           DMF        2 ml

DO NOT WRITE IN THIS MARGIN

10            The mixture of 48255-105-14,  $\omega$ -bromo toluenitrile and K<sub>2</sub>CO<sub>3</sub> in DMF  
           was stirred at 40°C for 5 hr, then cooled to RT, stirring was continued overnight,  
           (3 days). Et<sub>3</sub>SiH was added to the the reaction and the solution  
           was washed with H<sub>2</sub>O (two times), brine and dried over MgSO<sub>4</sub>.  
           Purification was performed by flash chromatography on silica gel, loaded  
           with crude, eluted with 8% C<sub>18</sub>DM in CH<sub>2</sub>Cl<sub>2</sub> with 0.2% NH<sub>4</sub>SCN. Pure  
           fractions were combined and evaporated to give a white foam.  
           HPLC showed small impurities. Purified again by flash column, loaded with  
           crude, eluted with 12% C<sub>18</sub>DM in EtOAc. Pure fractions were combined  
           and evaporated to give a foam.

15            48255-105-16

48255-105-16 was dissolved in C<sub>18</sub>DM. Et<sub>3</sub>SiH in EtOAc (1M) was  
           added. The mixture was stirred at RT for 30 min then  
           evaporated to dryness. 120 mg

48255-105-20

20            RQ 23496

MS (Minimix)

MS (Aldrich)

EA

DP

30            PK<sub>a</sub>

35

SIGNED

*[Signature]*

DATE -

WITNESSED AND  
UNDERSTOOD BY:

DATE

CROSS REFERENCES:

*[Signature]*  
ATTACHMENT I

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